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Influence of Hygroscopic Growth upon the Deposition of Bronchodilator Aerosols in Upper Human Airways

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THE INFLUENCE OF HYGROSCOPIC GROWTH UPON THE DEPOSITION OF BRONCHODILATOR AEROSOLS IN UPPER HUMAN AIRWAYS

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ABSTRACT

The influence of hygroscopic growth upon the behavior of two bronchodilator drugs in upper airways is studied with an aerosol deposition model. The latter accounts for laryngeal jet impaction and turbulent flow instabilities caused by the larynx in computing particle deposition efficiencies. Experimental growth rate data are used to define hygroscopic characteristics of the aerosols. The effect of growth following water vapor absorption and the influence of a humectant (glycerin) used in some therapeutic drugs are shown to be complex; whether the total dose deposited is increased or decreased is a function of initial particle size, rate of growth and inspiratory flow rate.

INTRODUCTION

It has been experimentally established that aerosol deposition efficiencies in the human are related primarily to the mass median aerodynamic diameters (MMAD) of the constituent particles, and are, relatively, not very dependent upon the geometric standard deviations (σ_g) of the size distributions (Task Group on Lung Dynamics, 1966; Morrow, 1974). Knowledge concerning the influence of hygroscopic growth upon particle deposition is, therfore, very important in the planning of aerosol therapy regimens. While experimental information about the significance of hygroscopic growth might be attained by direct measurement and comparison of the total dose, and intra-tracheobronchial (TB) distribution, of nonhygroscopic and hygroscopic aerosols of identical inspired sizes, unfortunately, such empirical data has not been reported.

In a recent investigation, Martonen (in press) has measured the deposition of nonhygroscopic particles in combined larynx-TB models. Total dose, intra-TB distribution of particulate matter, and "hot spots", or enhanced deposition sites, at airway bifurcations were quantitated. The experimental data established that replica larynx casts combined with single-pathway six generation TB models are a suitable surrogate system for studying aerosol behavior in upper human airways. Here, we shall use an established theoretical model to study the effect of hygroscopic growth upon the deposition of bronchodilator aerosols in upper human airways simulated by the experimental system.

The nature of a respiratory tract disease or injury is a major criterion in selection of the specific drug(s) to be used in treatment; and, the hygroscopic behavior of an inspired drug may be predetermined by its physicochemical properties. Since the MMAD of a hygroscopic aerosol may change as it travels through a humid environment it may have a different

dose distribution than a nonhygroscopic aerosol of identical inspired MMAD. Hence, initial particle sizes of these two different types of aerosol should be adjusted differently to produce selective deposition of airborne drugs at appropriate sites in the TB tree.

Bell and Ho (1981) have studied the growth rates of two therapeutic aerosols containing isoproterenol hydrochloride as the active bronchodilator agent. Mathematical descriptions of these hygroscopic growth curves were incorporated, as computer subroutines, into our analytical model which calculates the total deposition, and intra-TB dispersion, of deposited particles. Since this work focuses upon aerosol behavior within upper human airways, computations are normalized to the aerosol mass that penetrates the oropharyngeal compartment (for mouth breathing) and larynx. Enhanced losses that occur in the trachea due to the laryngeal jet and downstream airflow instabilites are accounted for in the model, as are losses due to turbulent airflow patterns in main, lobar and segmental bronchi. The findings will be useful in understanding the behavior of any dry therapeutic aerosols including micronized powders from hand-held, metered-dose cannisters.

AIRFLOW AND AIRWAY DESCRIPTIONS

Many efforts have been made to define the lengths, diameters and branching angles of the conducting airways of the human TB tree (for example, Findeisen, 1935; Weibel, 1963; Horsfield et al., 1971; Yeh et al., 1976). Furthermore, Horsfield and Cumming (1967) and Sudlow et al. (1971) have examined the radii of curvature at airway divisions and the geometries of carinae at bifurcations. The symmetric Model A presented by Weibel (1963) is a very simple, dichotomously dividing network whose airway

dimensions and number are based upon anatomical measurements. This TB description, with a branching angle of 70° at the bifurcation between two airways of the same generation as suggested by Horsfield and Cumming (1967), will be used here.

Turbulent airflow conditions are known to be generated at the larynx and to persist in downstream airways. Information actually quantitating laryngeal effects upon airflow patterns in the trachea and distal bronchi, however, is limited. This is unfortunate since the influence of disturbed airflow patterns upon the fate of inspired bronchodilator aerosols should not be ignored. The laminar to turbulent flow transition in replica casts and idealized models of the trachea and main bronchi that occurs due to the presence of the larynx, cartilagenous rings, and airway branching sites has been experimentally investigated by Dekker (1961), West and Hugh-Jones (1959), and Sudlow et al. (1971). Apparently, the glottic opening of the larynx which changes during breathing has two effects. First of all, to generate a laryngeal jet in the trachea as inspired air enters through a narrow slit. Secondly, to create airflow instabilities like turbulent eddies in upper airways as air diverges distal to the vibrating glottis. The airflow pattern used in a previous work (Martonen, 1982) to describe conditions in the human TB tree based on these experimental findings will also be used here. Therefore, laminar plug flow will be assumed in generation I = 4 and 5 airways distal to the segmental (I = 3) bronchi for all inspiratory flow rates, and the same will hold for the trachea and large bronchi ($0 \leq I \leq 3$) for an inspiratory flow rate less than 6 ℓmin^{-1} (the latter being the critical value for upper airway turbulence determined by Dekker (1961)). When that critical value is exceeded, however, as will be the case in this work, airflow in these upper airways will be turbulent.

AEROSOL DEPOSITION

Deposition of inhaled aerosols within conducting airways of the TB tree occurs when particulate matter comes into contact with, and is retained by, airway surfaces. In the upper human airways, airborne particulate matter (MMAD $\geq$ 1 μm) is directed toward bronchial walls primarily by the action of gravitational and centrifugal forces. The latter arise from the curved paths that inspired particles must follow in the bifurcating bronchial passages. Particle collection by impaction occurs at TB branching sites when particles of sufficient inertia do not follow fluid streamlines. Particle collection by sedimentation occurs when gravitational acceleration has a component directed toward the walls.

Martonen (1982) has presented a system of formulae to compute particle deposition efficiencies in human airways. When the action of the inertial impaction and sedimentation mechanisms are denoted as P(I) and P(S), respectively, total aerosol deposition efficiencies can be calculated from Landahl's (1950) superposition equation

$$P(T) = 1 - (1 - P(I))(1 - P(S)). \qquad (1)$$

Experimental data from aerosol deposition studies using both human and animal replica TB casts with and without appropriate replica larynx casts upstream have shown increased losses in the trachea when a larynx was present (Schlesinger and Lippmann, 1976; Lippmann and Altshuler, 1976). The pattern took the form of a "hot spot" of greatly enhanced deposition immediately distal to the larynx ascribed to the laryngeal jet, and increased losses downstream probably due to turbulent eddy action. Chan et al. (1978) have quantitated such enhanced tracheal losses in experiments.

The empirical formula given to describe increased probability of deposition in the human trachea, p(t), due to the larynx is

$$p(t) = 2.536\ Stk^{1.231}. \qquad (2)$$

Stk is the particle Stokes number defined by the relation $Stk = \rho D^2 V/18\mu R$ where μ is the viscosity of air, R is the trachea radius, V is the mean airstream velocity in the trachea, and ρ and D are the density and diameter of the particle, respectively. Equation (2) is valid for $Stk > .003$ which implies that the larynx effect may be quite significant for aerosols with MMAD's > 1μm. It is important to note that most clinical nebulizers used in aerosol therapy protocols generate polydisperse aerosols with much greater MMAD's. Including the effect of larynx-induced airflow instabilities in calculating administered dose of hygroscopic medicinal aerosols has not yet been reported in the open literature; we shall compute trachea losses by combining equation (2) with the P(I) equations of Martonen (1982). Use of the latter's P(I) and P(S) formulae derived for the turbulent airflow conditions in airway generations $0 \leq I \leq 3$ (trachea, main, lobar and segmental bronchi) noted previously will permit the effect of airflow instabilities in large bronchi to be quantitated also.

BRONCHODILATOR GROWTH RATES

Growth rates of some dry hygroscopic bronchodilator aerosols generated from 0.5% Isuprel^R and 1% Isuprel^R solutions have been measured at conditions approximating those in the upper human TB tree: 37°C temperature and 92% - 95% relative humidity (Bell and Ho, 1981). The mixing of dry

aerosol particles with water saturated air such as occurs in the trachea distal to the larynx was also simulated in the experimental system. The 0.5% Isuprel^{R} solution contains 0.5% isoproterenol hydrochloride as the active bronchodilator agent, as well as 8% glycerin and smaller quantities of sodium chloride, citric acid, sodium bisulfite and chlorbutanol. The 1% Isuprel^{R} solution contains 1% isoproterenol hydrochloride, no glycerin and small quantities of the aforementioned preservative and buffering chemicals. The addition of the humectant glycerin to the bronchodilator isoproterenol hydrochloride solution was shown to cause the 0.5% Isuprel^{R} aerosol to grow more slowly than the 1% Isuprel^{R} aerosol. Dry aerosols generated from the latter solution are expected to have growth rate characteristics in the lung similar to dry micronized powder aerosols of isoproterenol hydrochloride that contain no glycerin that are generated by some metered-dose devices.

The work of Bell and Ho (1981) showed that the growth rate of a medicinal aerosol particle in a fixed temperature and R.H. environment will depend upon its original chemical composition and initial size. Unless the particle sizes generated in aerosol therapy procedures can be precisely controlled, therefore, regulating breathing rates is the only way to preferentially deposit aerosols since growth rates themselves are physicochemical characteristics of the drugs. This may not be practical in every aerosol therapy laboratory or easy to accomplish, especially when treating the young or very ill. The alternative is to produce aerosols which are highly uniform in particles of a desired size prior to inhalation so that when subsequent growth occurs drugs can be selectively deposited. An advantage of the latter procedure is that losses in the oral pharyngeal compartment and the larynx can be minimized by generating initially small particles which penetrate those regions. Techniques to generate such

monodisperse aerosols are becoming standard in inhalation exposure studies with human test subjects (for example: Lippmann and Albert, 1969; Godfrey et al., 1974; Stahlhofen et al., 1979).

Air in the large conducting airways of anaesthetized patients has been shown to be in the range of 90%-95% R.H. (Dery et al., 1967). Ingolstedt (1956) has measured a relative humidity of 90% in the trachea of human subjects breathing through the mouth; the theoretical model of Ferron et al. (1982) predicts much higher values, approaching 98%. In distant peripheral regions of the lung R.H. values will certainly be very high, perhaps approaching 100% R.H. Ferron et al. (1982) have suggested that equilibrium temperature and R.H. values are attained in the 11th generation airways of Weibel's (1963) morphology. But Olson et al. (1973) have indicated that temperature in the trachea may be within 0.2°C of the 37°C equilibrium value found in the deep lung. Use of the empirical hygroscopic growth curves of Bell and Ho (1981) will be a good description of bronchodilator behavior in upper conducting airways and will become more approximate with progression to terminal bronchi.

DEPOSITION OF BRONCHODILATOR AEROSOLS

Bronchodilator aerosols are most commonly administered orally, and hygroscopic growth may be assumed to start at the trachea since negligible time is spent in the oral pharyngeal compartment when a bolus of aerosol is ejected from a pressurized, hand-held, metered-dose device. The time span available for hygroscopic growth prior to entering a specific TB airway generation, therefore, is the summation of the residence times spent in proximal generations. Hence, for a given inspiratory flow rate final particle diameters at prescibed positions in the TB tree can be determined

using the experimental growth curves. Corresponding final densities can easily be calculated if changes in size are attributed only to addition of water vapor. Therefore, the probability of deposition can be ascertained using the appropriate formulae (Martonen, 1982) since the necessary particle parameters will have been defined.

The aerodynamic particle size distributions of various different bronchodilator aerosol generators for personal use have been measured by Hiller et al. (1978). Particle sizes used here in TB deposition computations correspond approximately to the lower and upper aerodynamic size limits and a typical MMAD of those micronized powder aerosols.

Theoretical deposition patterns for particles of Dae(0) = 2 μm at trachea, generation I = 0, flow rates of Q(0) = 30 ℓmin^{-1}, 60 ℓmin^{-1} and 120 ℓmin^{-1} are given in Figure 1. For a given flow rate, the regional distribution of particulate matter deposited in the upper airways does not vary considerably as evidenced by the similar forms of the deposition graphs. The magnitudes of total doses deposited can be determined by summation of the respective graphs over the six airway generations, $0 \leq I \leq 5$. Significantly, total deposition efficiencies do not always increase with particle hygroscopicity. For example, total deposition for the bronchodilator with glycerin (0.5% Isuprel^R) is slightly less than that for nonhygroscopic particles of identical inhaled aerodynamic size, about 8% and 10%, respectively, at the highest Q(0) value. This may be attributed to a reduction in Dae of such particles upon inhalation as discussed below.

The variation of 0.5% Isuprel^R particle aerodynamic size with upper TB location is illustrated in Figure 2 for the 120 ℓmin^{-1} inspiratory flow rate. For a spherical droplet of geometric diameter d and material density ρ, it follows from the definition of aerodynamic diameter that $Dae = \sqrt{\rho}\, d$. For the glycerin containing particles a decrease in particle density with

the absorption of water vapor offsets the initial increase in geometric size producing a smaller aerodynamic size than the original. These particles are reduced from Dae(0) = 2 μm to Dae(1) = 1.86 μm upon leaving the trachea and entering the main bronchi, (I = 1). Although Dae increases monotonically thereafter, theoretical considerations indicate that a particle will leave the upper airways with an aerodynamic size < 2 μm. For 1% Isuprel^R particles, however, hygroscopicity results in total deposition being increased relative to nonhygroscopic particles at all flow rates. Indeed, on the basis of calculations for 60 ℓmin^{-1}, total bronchodilator deposition will be 14%, an enhancement of 40% relative to the nonhygroscopic aerosol. The variation in aerodynamic size of the latter bronchodilator particles, as may be experienced in the larynx-TB system of Martonen (in press), are also shown in Figure 2.

Figure 3 shows the deposition patterns calculated for Dae(0) = 1 μm, 2 μm and 4 μm particles entering the trachea at an inspiratory flow rate of Q(0) = 60 ℓmin. Total deposition efficiencies increase with aerosol hygroscopicity for the 1 μm and 2 μm particles (for sake of clarity the 0.5% Isuprel^R data are not shown). The situation is different, however, for the 4 μm particles as the graphs of Figure 3 illustrate; total deposition was less for the hygroscopic bronchodilator aerosol containing glycerin than for the nonhygroscopic aerosol. For the 4 μm particles, total 1% Isuprel^R aerosol mass deposition will be increased by a factor of 1.22, from 18% to 22%, compared to nonhygroscopic particles due to water vapor absorption such as may occur in upper airways of the lung, and in a humidified larynx-TB system to be used in future experimental work. The effect of hygroscopic growth is, of course, more marked when all 16 generations of conducting airways of the TB network are considered. Total deposition of the nonhygroscopic, 0.5% Isuprel^R, and 1% Isuprel^R aerosols for this case

(Dae(0) = 4 μm and Q(0) = 60 ℓmin^{-1}) are 74%, 70% and 95%, respectively. Calculations indicate that a 0.5% Isuprel^{R} particle will not regain its original aerodynamic size until entering the terminal generation of airways; at that point, a 1% Isuprel^{R} particle will have grown to 5 μm in aerodynamic size. For the upper airways, theory suggests that the addition of glycerin to the isoproterenol hydrochloride solution will decrease total deposition to 15% which is, relatively, a 32% reduction in drug dose. As before, this decrease in mass collected upon hygroscopic growth can be ascribed to a reduction in particle Dae upon introduction to a humid atmosphere. For 4 μm particles this was observed at many flow rates, for example, the variation of Dae for the two bronchodilator aerosols at Q(0) = 30 ℓmin^{-1} is also illustrated in Figure 2. For a given particle size the influence of hygroscopic growth and glycerin upon the distribution of aerosol mass within the upper airways does not appear to be too significant as suggested by the similar forms of the graphs in Figure 3.

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REFERENCES

Bell, K.A. and Ho, A. (1981) J. Aerosol Sci. 12, 247.

Chan, T.L., Lippmann, M., Cohen, V.R., and Schlesinger, R.B. (1978) J. Aerosol Sci. 9, 463.

Dekker, E. (1961) J. Appl. Physiol. 16, 1060.

Dery, R., Pelletier, J., Jacques, A., Clavet, M., and Honde, J.J. (1967) Can. Anaesth. Soc. J. 14, 287.

Ferron, G.A., Kreyling, W., and Haider, B. (1982) J. Aerosol Sci. 13, 161.

Findeisen, W. (1935) Pflüger Arch. fd. ges. Physiol. 236, 367.

Godfrey, S., Zeidfard, E., Brown, K., and Bell, J.H. (1974) Clin. Sci. Molec. Med. 46, 265.

Hiller, C., Mazumder, M., Wilson, D., and Bone, R. (1978) Am. Rev. Respir. Dis. 118, 311.

Horsfield, K. and Cumming, G. (1967) Bull. Math. Biophys. 29, 245.

Horsfield, K., Dart, G., Olson, D.E., Filley, G.F., and Cumming, G. (1971) J. Appl. Physiol. 31, 207.

Ingolstedt, S. (1956) Acta Oto-Laryng. Suppl. 131.

Landahl, H.D. (1950) Bull. Math. Biophys. 12, 43.

Lippmann, M., and Albert, R.E. (1969) Am. Ind. Hyg. Assoc. J. 30, 257.

Lippmann, M., and Altshuler, B. (1976) Air Pollution and the Lung, (Edited by Aharonson, E.F., et al.) Wiley and Sons, New York.

Martonen, T.B. (1982) Bull. Math. Biol. 44, 425.

Martonen, T.B. J. Aerosol Sci. (in press).

Morrow, P.E. (1974) Am. Rev. Respir. Dis. 110, 88.

Olson, D.E., Sudlow, M.F., Horsfield, K., and Filey, F.F. (1973) Arch. Intern. Med. 131, 51.

Schlesinger, R.B., and Lippmann, M. (1976) Thorax 31, 678.

Stahlhofen, V.W., Gebhart, J., Heyder, J., and Stuck, B. (1979)

Staub-Reinhalt. Luft. 39, 73.

Sudlow, M.F., Olson, D.E., and Schroter, R.C. (1971) Inhaled Particles III (Edited by Walton, W.H.) Unwin, Surrey, England.

Task Group on Lung Dynamics (1966) Health Phys. 12, 173.

Weibel, E.R.(1963) Morphometry of the Human Lung, Springer-Verlag, Berlin.

West, J.B., and Hugh-Jones, P. (1959) J. Appl. Physiol. 14, 753.

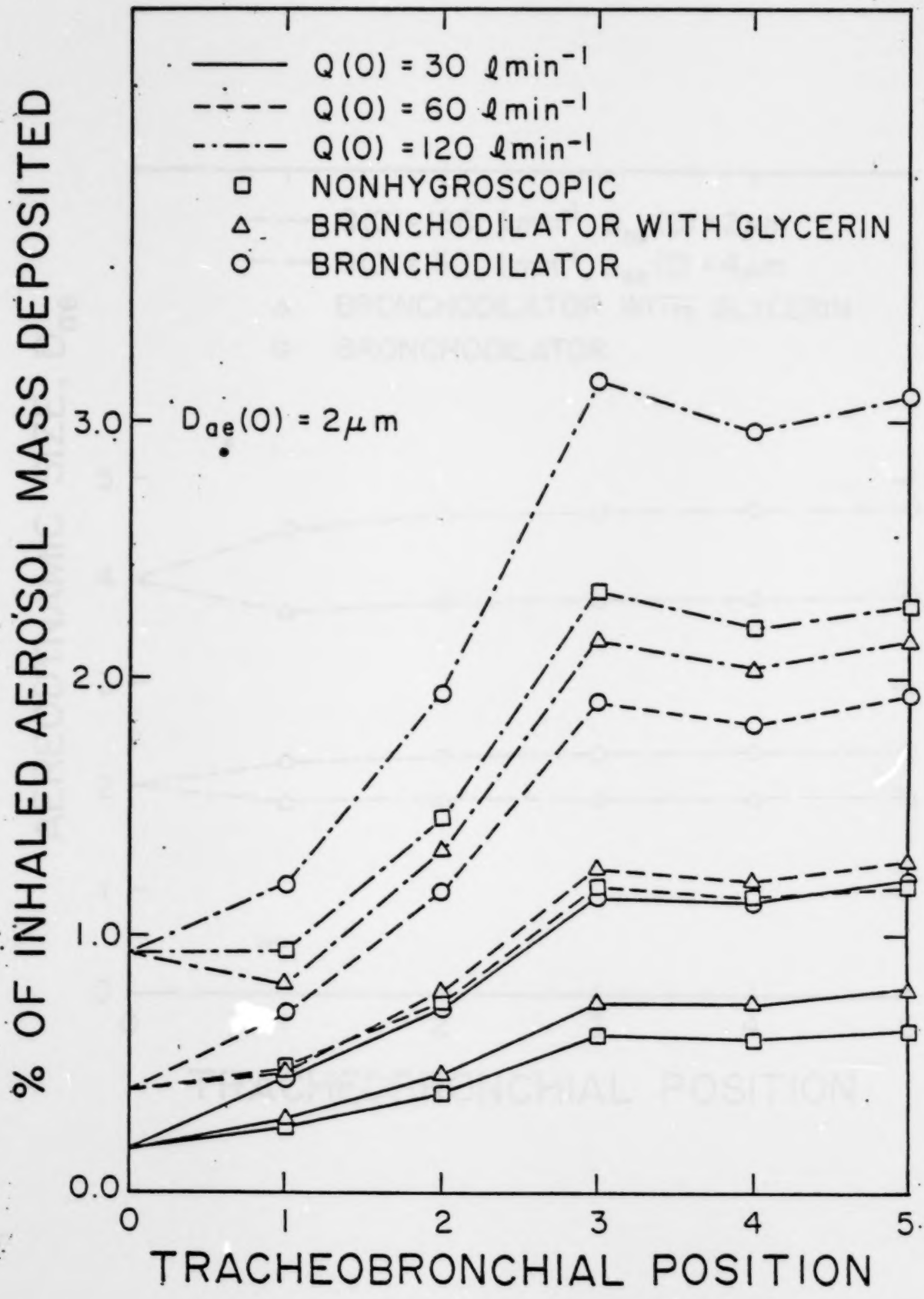
Yeh, H.C., Phalen, R.F., and Raabe, O.G. (1976) Environ. Health Perspec. 15, 147.

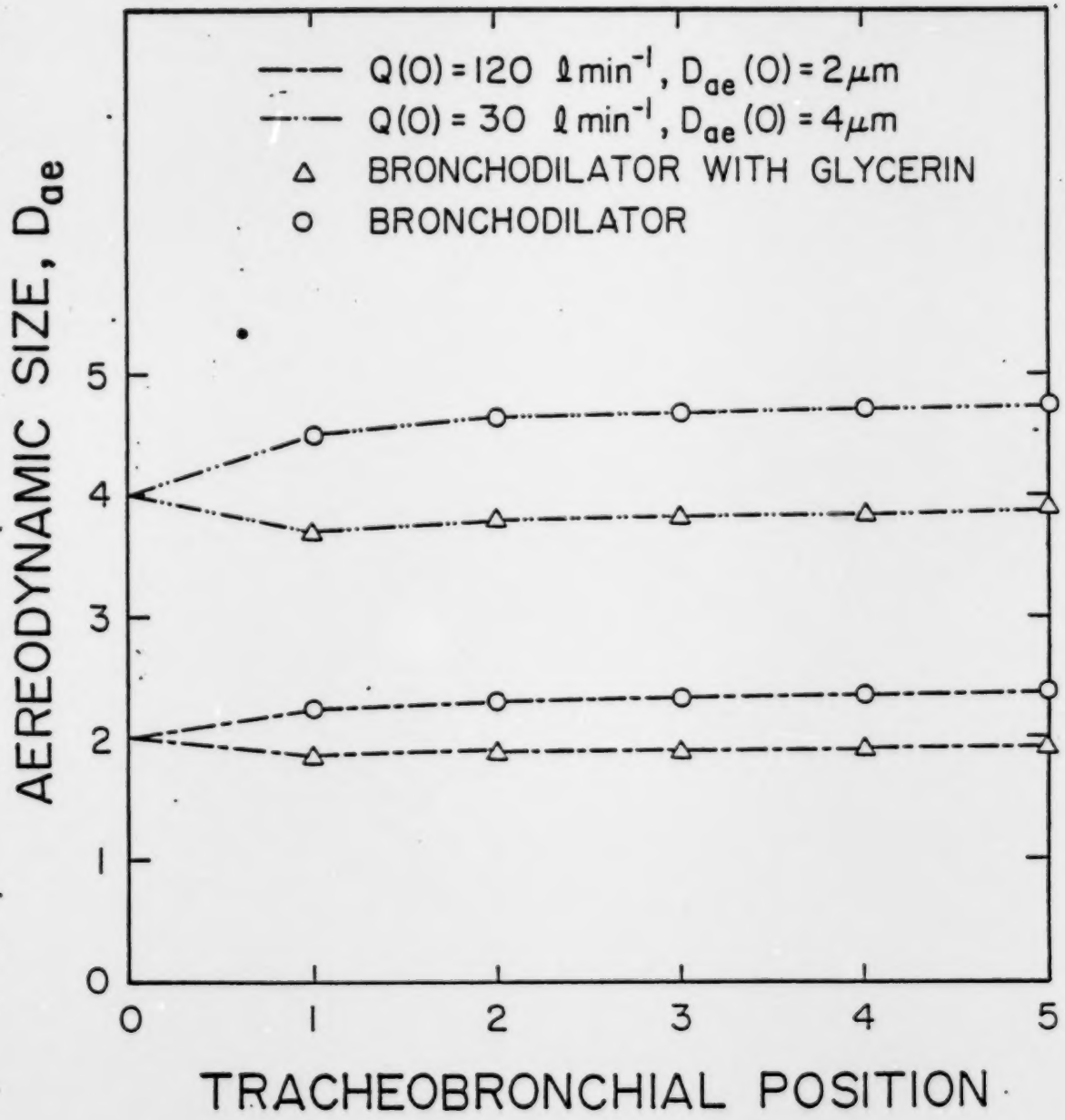
LEGENDS OF FIGURES

Figure 1. Aerosol dose distribution patterns. Hygroscopic aerosols change in size according to Bell and Ho (1981) empirical curves. Effect of the laryngeal jet is described by equation (2).

Figure 2. Variation in aerodynamic diameter of hygroscopic bronchodilator particles with progression through upper airways.

Figure 3. Aerosol dose distribution patterns. Hygroscopic aerosols change in size according to Bell and Ho (1981) empirical curves. Effect of the laryngeal jet is described by equation (2).


Q(0) = 30 ℓmin⁻¹
Q(0) = 60 ℓmin⁻¹
Q(0) = 120 ℓmin⁻¹
NONHYGROSCOPIC
BRONCHODILATOR WITH GLYCERIN
BRONCHODILATOR
$D_{ae}(0) = 2\mu m$
% OF INHALED AEROSOL MASS DEPOSITED
0.0
1.0
2.0
3.0
0
1
2
3
4
5
TRACHEOBRONCHIAL POSITION


Q(0) = 120 ℓ min⁻¹, D_{ae} (0) = 2μm
Q(0) = 30 ℓ min⁻¹, D_{ae} (0) = 4μm
BRONCHODILATOR WITH GLYCERIN
BRONCHODILATOR
AEREODYNAMIC SIZE, D_{ae}
0
1
2
3
4
5
TRACHEOBRONCHIAL POSITION